EXHIBIT 3

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Division of Dockets Management Branch (HFA-305)
Food and Drug Administration
Room 1061
5620 Fishers Lane
Rockville, MD 20852

Re: Docket No. 2005P-0127 (CP1): Leflunomide

Kali Laboratories, Inc. (Kali) holder of ANDA 77-086 for Leflunomide Tablets 10 mg and 20 mg, hereby submits the following comments in opposition to the above-referenced citizen petition recently filed by Aventis Pharmaceuticals. Kali Laboratories, Inc. is a wholly-owned subsidiary of Par Pharmaceutical Companies.

A. Aventis' Petition is an Eleventh-Hour Attempt to Delay Approval of Generic Formulations of ARAVA

Plainly, Aventis' petition, filed on March 31, 2005 near the end of FDA's review period for a number of ANDAs for generic formulations of Arava (leflunomide), is intended solely to delay generic competition to Arava. Aventis' petition must be viewed and ruled on in this light. Moreover, Aventis' contentions are spurious and are not germane to the issue at hand. There are two major flaws of concept in their argumentation: 1) generic products can obtain approval for all or part of a range of dosage strengths for a product, and 2) the current labeling for Arava contains information that allows for initiation of therapy with the lower dosage strengths and suggests that they may be preferable in certain clinical situations.

B. ANDA Applicants Need Only Meet Approval Requirements for Selected Dosage Strengths

FDA considers each dosage strength of a listed drug to be a separate and distinct drug product requiring ANDA approval. (Preamble to Final ANDA Regulations, 57 Fed. Reg. 17950, 17954 (April 28, 1992). FDA has long permitted an ANDA applicant to receive approval to market certain, but not all, dosage strengths of a listed drug, based upon fulfillment of the approval requirements for those particular strengths.

Here, Kali seeks approval to market the 10 mg and 20 mg dosage strengths of Leflunomide Tablets. Accordingly, Kali is only required to meet the regulatory requirements for these strengths.

There is certainly ample precedent for this situation. In a recent example, FDA has approved Teva Pharmaceuticals' drug product Oxycodone Hydrochloride ER Tablets 80 mg, even though the listed drug, Purdue Pharma's Oxycontin, is available in 10 mg, 20 mg, 40 mg, 80 mg, and 160 mg strengths. The other dosage strengths lower and higher than 80 mg and are available for individualized titration to the dosage with adequate effect (see pertinent pages of Purdue packaging insert in Attachment 1and Teva package insert in Attachment 2). Yet Teva is not required to, and does not, market those other strengths.

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C. Initiation of Therapy / Recommended Lower Dosage Strengths

The Dosage and Administration section of the Arava labeling (see Attachment 3) states " ...It is recommended that Arava therapy be initiated with a loading dose of one 100 mg tablet per day for 3 days. Elimination of the loading dose regimen may decrease the risk of adverse events. This could be especially important for patients at increased risk of ...". From this it is clear that the current labeling suggests settings in which the 100 mg dosage strength may not be desirable and in fact should not be used.

In fact, this loading dose strategy, 100 mg /day for 3 days, is likely to be beneficial only to those patients who need a rapid loading dose strategy and thus need to be exposed to an increased risk of adverse effects for this reason.

Significantly, the recommended maintenance dose of Leflunomide Tablets is 20 mg daily, and the approved labeling states that "doses higher than 20 mg/day are not recommended." (See Arava's labeling, Attachment 3). To require generic applicants to develop and seek approval of 100 mg strength, solely to provide a more rapid loading dose, is irrational.

With Leflunomide Tablets, the 100 mg strength is available from another source (i.e., Aventis), and prescribing physicians can consult the labeling of the Arava package insert for loading dose information using that strength.

FDA could consider requesting a statement in generic product labeling directing physicians to the Arava labeling for loading does information (although this has not been required in other situations, such as the Oxycodone Hydrochloride ER Tablets example noted above).

D. Due to Discontinued Marketing, ARAVA 100 mg Tablets Are Unavailable

In addition to the above points the agency has several other considerations. Aventis' citizen petition would require ANDA applicants for generic formulations of Leflunomide Tablets, 20 mg to conduct an additional *in vivo* bioequivalence study to obtain regulatory approval, namely, a study showing that five 20 mg tablets are bioequivalent to one 100 mg tablet, on the ground that the labeling for Arava recommends 100 mg daily for three days as a loading dose to achieve a steady-state concentration. Such a study would be over and above the required *in vivo* bioequivalence study showing that a generic formulation of Leflunomide Tablets, 20 mg is bioequivalent to Arava tablets, 20 mg.

This additional hurdle would not only be contrary to FDA's policy of allowing ANDA applicants to meet approval requirements for selected dosage strengths of a listed drug (see section B, *supra*), but also would present an impracticable task. On information and belief, Aventis has discontinued the commercial marketing of Arava 100 mg tablets in the United States. This is evidenced by the July 2004 "Additions/Deletions" page of FDA's Electronic Orange Book, which states that 100 mg dosage strength of Arava is deleted (see Attachment 4).

To Kali's knowledge, Aventis is marketing only the 10 and 20 mg tablet strengths of leflunomide, which are the listed drug products upon which Kali has based its ANDA. Upon further information and belief, Aventis currently provides ARAVA 100 mg tablets only in blister pack product samples requested by physicians (see enclosed IMS sample data in annexed Attachment 5).

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Accordingly, the lack of access to the 100 mg strength caused by Aventis' own cessation of marketing, coupled with the obvious impracticality of procuring the 100 mg strength from doctors, render it impossible for generic applicants such as Kali to obtain sufficient dosage units of the reference branded product to be able to conduct the further bioequivalence study that Aventis proposes. (In effect, Aventis would have FDA impose a regulatory requirement that would prevent the approval of generic versions of Arava 10 mg and 20 mg tablets, unless the sponsors of applications for such drug products conduct a second bioequivalence study that is not feasible). FDA should not acquiesce in this obvious "Catch-22" situation.

For all the foregoing reasons, Aventis' petition should be summarily denied. FDA should reject Aventis' transparent attempt to hinder the availability of low-cost generic versions of Leflunomide Tablets to Americans suffering from such a debilitating disease as rheumatoid arthritis.

Sincerely,

W. Scott Groner
Associate Director Regulatory Affairs

cc: Gary J. Buehler (OGD Director)